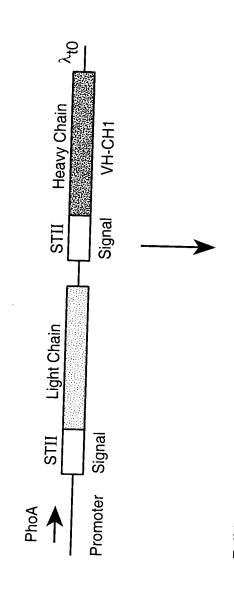
e green, green, week, green, wasse, green, green, green, green, week, green, gr

Fab Expression Vector pAK19



Full Length Antibody Expression Vector Derived from pAK19

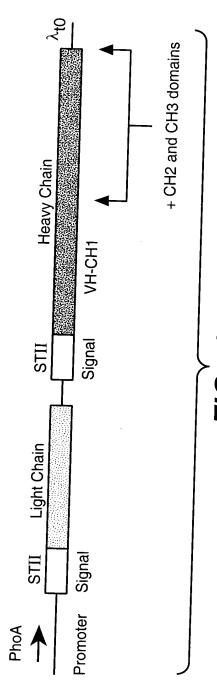


FIG._1

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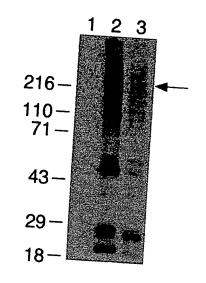


FIG._2

Polycistronic Constructs

		• -		istructs	
AP Promoter	STII	Light Chain	STII	Heavy Chain	^λ t0 Trans. Term.
L	TIR		TIR		
;	1 3 I		1 1 3	paTF20 paTF30	
3 7	•		3	paTF40 paTF90 paTF110	
7			7 7	paTF100 paTF120	
		FIA	\	1.3°	

FIG._3

polycistronic reduced

gi 1L 3L 1L 3L 7L 3L 7L E 1H 1H 3H 3H 3H 7H 7H

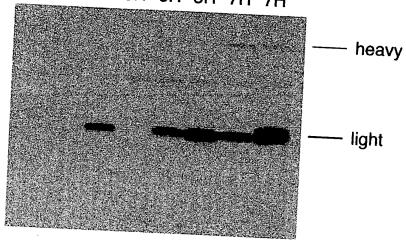


FIG._4A

polycistronic non-reduced

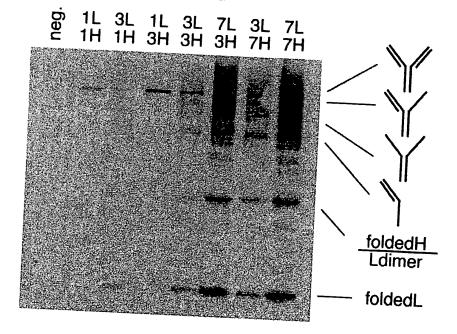
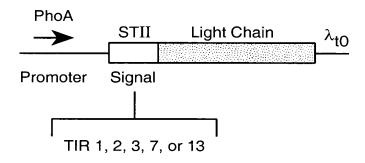


FIG._4B

Light Chain Constructions



Heavy Chain Constructions

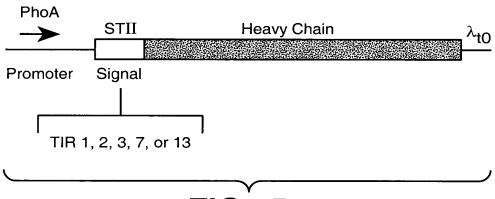
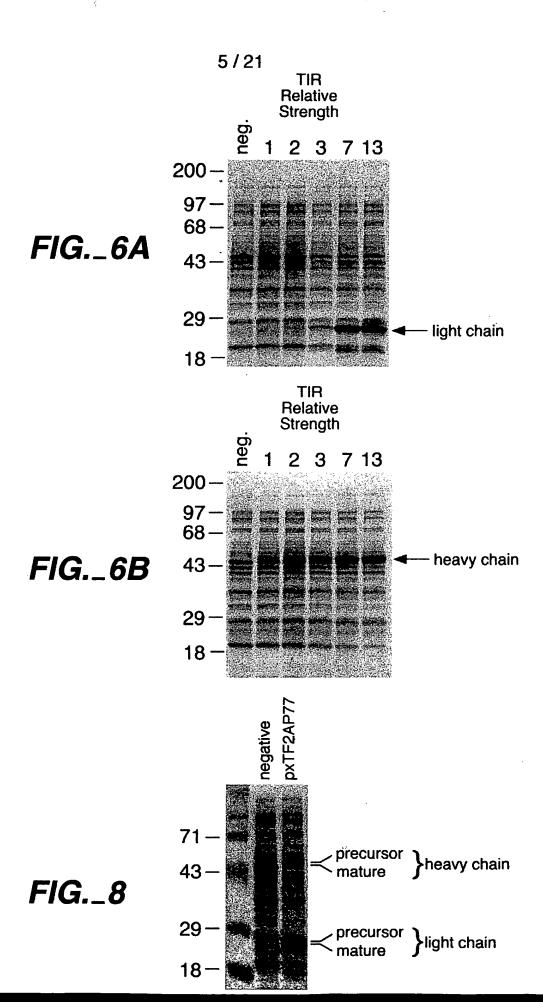
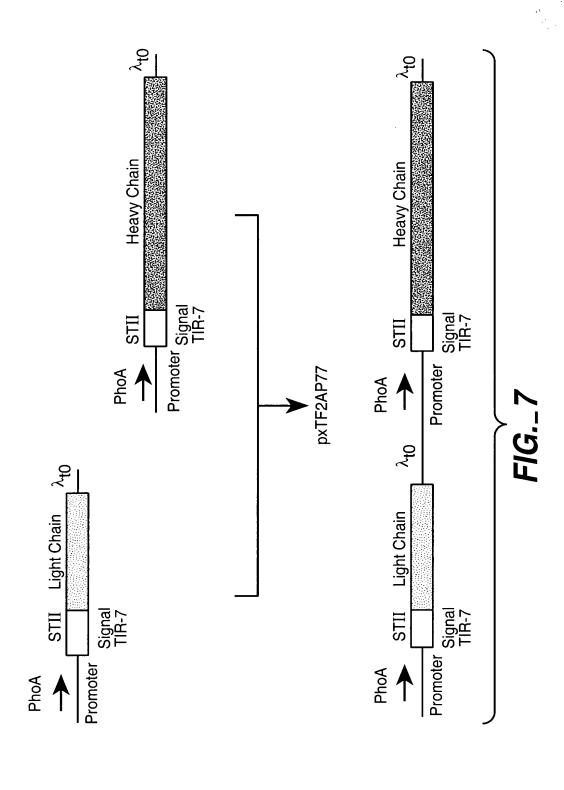


FIG._5





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Separate Cistron Constructs

AP Promoter	STII	Light Chain	λ _t 0 Trans. Term.	AP Promoter	STII	Heavy Chain	λt0 Trans. Term.
	IR				TIR		
·	1				1	paTF50	
	3				1	paTF70	
	1				3	paTF60	
	3				3	paTF80	
	7				3	paTF130	
	3				7	paTF140	
	7				7	paTF2AP77	

FIG._9

separate cistrons reduced

gi 1L 3L 1L 3L 7L 3L 7L E 1H 1H 3H 3H 3H 7H 7H

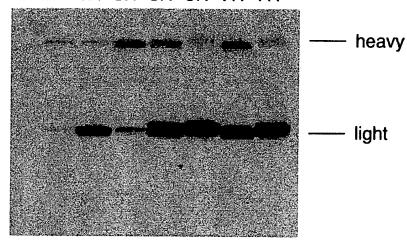
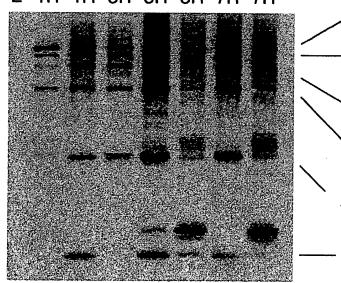


FIG._10A

separate cistrons non-reduced

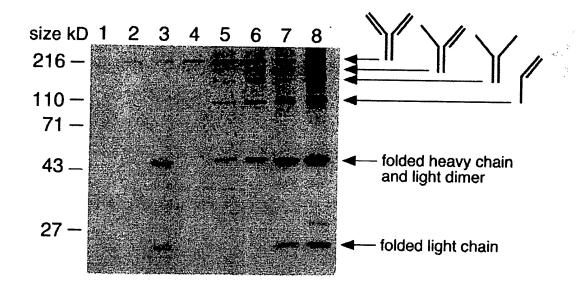
항 1L 3L 1L 3L 7L 3L 7L 일 1H 1H 3H 3H 3H 7H 7H



foldedH Ldimer

foldedL

FIG._10B



- 1) negative control
- 2) TIR 1-light, TIR 1-heavy, polycistronic
- 3) TIR 3-light, TIR 1-heavy, polycistronic
- 4) TIR 1-light, TIR 3-heavy, polycistronic
- 5) TIR 1-light, TIR 1-heavy, separate cistrons
- 6) TIR 1-light, TIR 3-heavy, separate cistrons
- 7) TIR 3-light, TIR 1-heavy, separate cistrons
- 8) TIR 3-light, TIR 3-heavy, separate cistrons

FIG._ 11

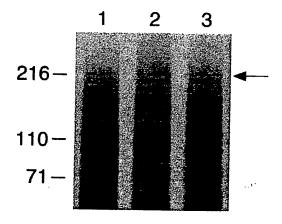
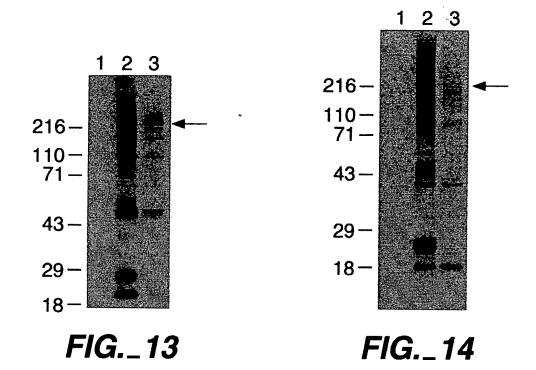
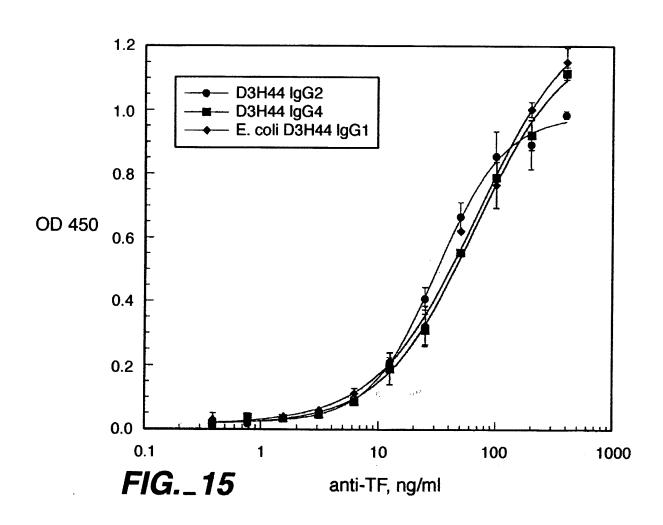
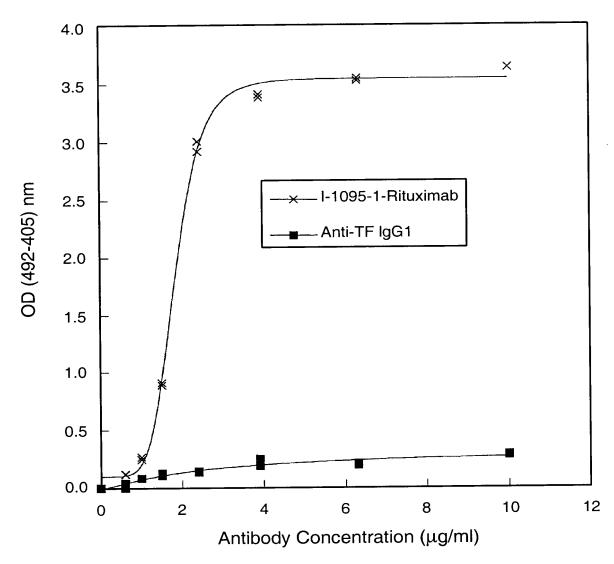


FIG._12







. At terms to the transport profession of the transport profession of the transport profession to the transport profession that the transport transport the transport profession to the transport tr

FIG._16

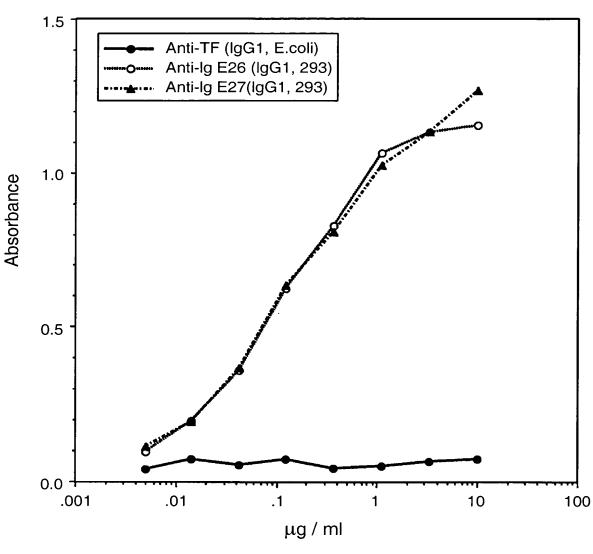


FIG._17

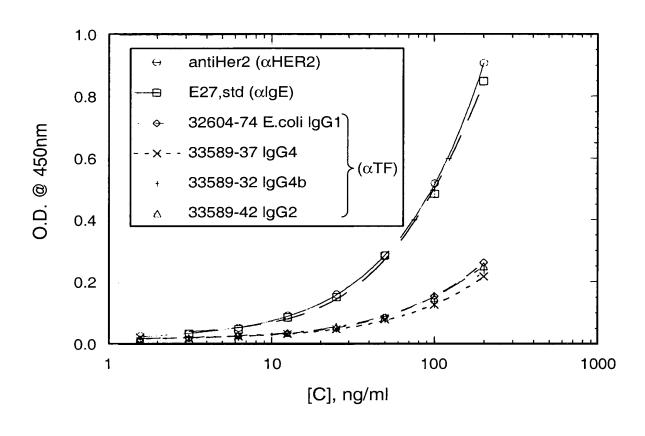


FIG._18

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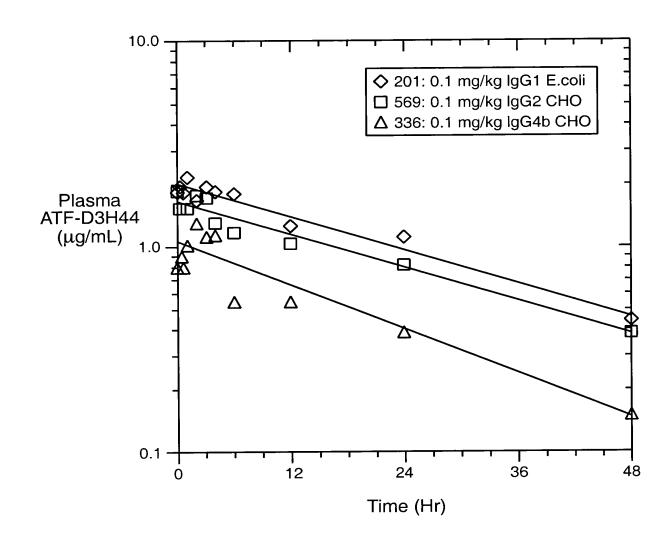


FIG._19

and the state of t

- |--

- GAATTICAACT TCTCCATACT TTGGATAAGG AAATACAGAC ATGAAAAATC TCAITIGCTGA GTTGTTATTT AAGCTTGCCC AAAAAGAAGA AGAGTCGAAT CFTBAGTTGA AGAGGTATGA AACCTATTCC TTTATGTCTG TACTTTTTAG AGTAACGACT CAACAATAAA TTCGAACGGG TTTTTCTTCT TCTCAGCTTA
 - GAACTIGIGIG CGCAGGIAGA AGCITTIGGAG AITIATICGICA CIGCAAHGCT TCGCAATATG GCGCAAAAHG ACCAACAGCG GITIGAITGAT CAGGIAGAGG CITIGACACAC GCGICCATCT ICGAAACCIC TAATAGCAGT GACGITTACGA AGCGITTATAC CGCGITTITAC IGGITGICGC CAACTAAATA GICCATCICC
 - GOSCIGITA CGAGGIDAAG CCCGAIGCCA GCAITICCIGA CGACGAIAGG GAGCIGCIGC GCGAITACGI AAAGAAGITA ITGAAGCAIC CICGICAGIA CCCGCGACAI GCICCAITIC GGGCIACGGI CGIDAAGGACI GCIGCIAIGC CICGACGACG CGCIDAIGCA ITICIICAAI AACIICGIAG GAGCAGICAI 201
- CGACAGTAITI ICAACAGIGC CGGCICIGAA IAITCAGCGAA ACAAAAAIAA AAAAITIACAI AAACAITIGAI CAIGCGITCA 301 AAAAGITAAT CITITCAACA GCIGICATAA AGIIGICACG GCCGAGACIT ATAGICGCIT IGITITIBAT TITIBAIGTA TITGIAACIA GIACGCAAGI TITITCAAITIA GAAAAGIITGI
- AGUCCATITI TOCCATAGAT CITTATRACTA CGTAAAGAAG AACGTAGATA CAAGCAAAAA AGATAACGAT GTITGCGCAT GCGACTATAG M K K N I A F L L A S M F V F S I A T N A Y A D I 401 TCACGTAAAA AGGGTATCTA GAATTATGAA GAAGAATATC GCATTTTCTTC TTGCATCTAT GFTCGFFFTT TCTAFTGCTA CAAACGCGTA CGCTGATATC Anti-Tissue Factor Light Chain^ ASTII Signal Sequence TIR~1
- CAGOGCIIGIA GITICIOGATA GACTIGACCA R D I K S Y L N W Y 501 CAGATGACCC AGTCCCCGAG CTCCCTGTCC GCCTCTGTGG GCGATAGGGT CACCATCACC TGCAGAGCCA GTCGCGACAT CAAGAGCTAT CTGAACTGGT GTCTACTGGG TCAGGGGCCTC GAGGGACAGG CGGAGACACC CGCTATCCCA GTGGTAGTGG ACGTCTCGGT CAGGGCTGTA GTTCTCGATA GACTTGACCA 26 Q M T Q S P S S L S A S V G D R V T I T C R A S R D I K S Y L N W Y
- 15/ 21 601 ATCAACAGAA ACCAGGAAAA GCTCCGAAAG TACTGATTTA CTATGCTACT AGTCTCGCTG AAGGAGTCCC TTCTCGCTTC TCTGGATCCG GTTCTGGGAAC TAGTTGTCTT TGGTCCTTTT CGAGGCTTTC ATGACTAAAT GATACGATGA TCAGAGCGAC TTCCTCAGGG AAGAGCGAAG AGACCTAGGC CAAGACCTG 60 Q Q K P G K A P K V L I Y A T S L A E G V P S R F S G S G T
- CTCAGAGGTA CCTGTAAACC TGTCCCATGG ESPWTFGO GAGICTCCAT GGACATTTGG ACAGGGTACC GGAITTACACT CTGACCATICA GCAGTICTGCA GCCAGAAGAC TTCGCAACTT ATTACTGTCT TCAGCACGGA CCTAATGTGA GACTGGTAGT CGTCAGACGT CGGTCTTCTG AAGCGTTGAA TAATGACAGA AGTCGTGCCT D Y T L T I S S L Q P E D F A T Y Y C L Q H G 93 701
- OCATICTICTIC TCATICTTCCC GCCATICTGAT GAGCAGTTGA AATCTGGAAC TGCTTCTGTT GTGTGCCTGC GGTAGACAGG CGGTAGACTA CTCGTCAACT TTAGACCTTG ACGAAGACAA CACACGGACG P S V V C L L 801 AAGGIGGAGA ICAAACGAAC IGIGGCIGCA CCAICIGICI TICCACCICT AGITIGCITG ACACCGACGI V A A H
- 901 TGAATAACIT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC GCCCTCCAAT GGGTAACIT CCAGGAGAGT GTCACAGAGC AGGACAGCAAA ACTTATTGAA GATAGGGTCT CTCCGGTTT CACTGTCTT CCACCTATTG CGGGAGGTTA GCCCATTGAG GGTCCTCTCA CAGTGTCTC TCCTGTCGTT > E S O Z U മ A L Q N O N Q W K EAK Y P R

TACAGOCTICA GCAGCACCCT GAGGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTICTAC

AIGICGGAGT CGICGIGGGA CIGCGACTCG

1001 GGACAGCACC CCTGTCGTGG

TITICGICIGA IGCICITIGE GITICAGAIG

GCCTGCGAAG TCACCCATCA GGGCCTGAGC CGCACGCTTC AGTGGGTAGT CCCGGACTCG

- CAAAGAGCIT CAACAGGGGA GAGIGITIAAT TAAATCCTCT AGGCGGACG CAITGIGGGG AGCTCGGTAC CCGGGGATCT AGGCCTAACG GITTICTCGAA GITGTCCCCT CTCACAATTA AITTIAGGAGA TGCGGCCTGC GTAGCACCGC TCGAGCCATG GGCCCCTAGA TCCGGAITTGC ø ں ھ K V Y E K H × K A D Ø ST А
 - O い 日 N R G മ × 1101 TCGCCCGTCA AGCGGGCAGT

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TGCAATGCTT	GACGATACGG	CCGAGACTTA	CATTICTICT GIBABGAGA F L L tence TIR-1
TTATICGTICAC AATTAGCAGTG	CATTICCTIGAC GTAAGGACTG	GTTGTCACGG CAACAGTGCC	YATGAAG AAGAATATCG CATTTCTTCT VIACTTC TTCTTATAGC GTAAAGAAGA M K K N I A F L L ^STII Signal Sequence TTR~1
GCTTTGGAGA CGAAACCTCT	CCGATGCCAG	CTCTCATAAA GACAGTATTT	AATTATGAAG TTAATACTTC M K ^STII
GCAGGTAGAA CGTCCATCTT	GAGGTAAAGC	AGCIGCIGC GGAITACGIA AAGAAGITAI IGAAGCAICC ICGICAGIAA AAAGITAAIC ITITCAACAG CIGICAIAAA GIIGICACG CCGAGACITA ICGACGACGC GCIAAIGCAI ITCIICAAIA ACIICGIAGG AGCAGICAII ITICAAIIAG AAAAGIIGIC GACAGIAITI CAACAGIGCC GGCICIGAAI	TAGTOGCTITI GITITITAITIT TITTAALGIPAT TIGIPAACIPAG TACGCAAGIT CACGIPAAAA GGGIBAICIPAG AAITTATGAAG AAGAATAACG CAITICITICI ATCAGCGAAA CAAAAATAAA AAAITACATA AACATIGATC AIGCGITCAA GIGCAITITIT CCCATAGAIC TTAATACITC TICITAATAGC GIAAAGAAGA M K K N I A F L L ^STII Signal Sequence TIR-1
AACTIGTIGTIGC TTGACACACG	GCCCTGTAC	AAAGITTAATC TITCAAITTAG	CACGTAAAA GIGCAITIITI
ATCTCGAATG TAGAGCTTAC	AGGIAGAGGG TCCATCTCCC	TCGTCAGTAA AGCAGTCATT	TACGCAAGIT AIGCGIICAA
CCCCACCCCC	TTGATTGATC AACTAACTAG	TGAAGCATCC ACTTCGTAGG	TTGTAACTAG AACAITGAIC
TITITATIGIT AAAATAACAA	CCAACAGCGG	AAGAAGITIAT TICITICAAIA	Tittaaigiai Aaaittacata
GCCGGGCGTT	CGCAAAATGA GCGTTTTTACT	CCALTACGIA GCIAAIGCAI	Gittitatit Caaaaataaa
1201 CTOGGTIGOC GCOGGCGTT TITITATIGIT GCCGACGCGC AICTICGAAIG AACTIGIGGG GCAGGTAGAA GCTITIGGAGA TITATICGTCAC TGCAAIGCTA GAGCCAACG CGCCCAACGG CGCCCAACGG CGCCCAACGG CGCCCAACGG CGCCCAACGG CGCCCAACGA AAAATAACAA CGGCTGCGCG TAGAGCTTAC TITGACAACG CGTCCAICTT CGAAACCTCT AATAGCAGTG ACGTTACGAA	1301 OGCAATANGG OGCAAAANGA CCAACAGGGG TIGATIGANC AGGTAGAGGG GGOGCIGTAC GAGGTAAAGC OCGAIGCCAG CAITOCTIGAC GACGATACGG GCGTIATACC GCGTIATACCACACCACCACACCACACCACACCACACACCACACACA	1401 AGCTGCTGCG CGATTACGTA AAGAAGTTAT TGAAGCATCC TCGTCAGTAA AAAGTTAATC TTTTCAACAG CTGTCATAAA GTTGTCACGG CCGAGACTTA TCGACGACGC GCTAATGCAT TTCTTCAATA ACTTCGTAGG AGCAGTCATT TTTCAATTAG AAAAGTTGTC GACAGTATTT CAACAGTGCC GGCTCTGAAT	1501 TAGICGCITT GITITIAITT TITAAIGIAI TIGIAACIAG TACGCAAGIT CACGIAAAAA GGGIAICIAG AAITAIGAAG AAGAATAICG CAITICITICI ATCAGCGAAA CAAAAAIAAA AAAITACAIA AACAIIGAIC AIGCGIICAA GIGCAITITI CCCAIAGAIC IIAAIACIIC TICITAIAGC GIAAAGAAGA 1 1 A F L L A F L L A F L L A F L L A F L L A F L L A F L L L A F L L L A F L L L A F L L L L
1201	1301	1401	1501

1601 TGCATCTATG TICGITITITI CTATIGCTAC AAACGCGTAC GCTGAGGTIC AGCTGGTGGA GTCTGGCGGT GGCCTGGTGC AGCCAGGGG CTCACTCCGT ACGTAGATAC AAGCAAAAA GATAACGATG TITGCGCATG CGACTCCAAG TCGACCACCT CAGACCGCCA CCGGACCACG TCGGTCCCCC GAGTGAGGCA Д U ^Anti-Tissue Factor Heavy Chain U თ დ I > O **户** ď 4 Z н Ø Ŀ > [z₄ Ŋ

16/21 1701 THEFOCTIONE CAGCITICIOS CHICAATATH AAGGAGIACH ACAUGCACHG GOTCCOFICAG GCCCCGGGTA AGGGCCTIGGA ATGGGTTIGGA THGAITHGAIC AACTAACHAG GCCCCGGACAC TICCCGGACCT TACCCAACCT AACTAACHAG AACAGGACAC TICCCGGACCT TACCCAACCT AACTAACHAG 1801 CAGAGCAAGG CAACACGATC TATGACCCGA AGTTCCAGGA COGTGCCACT ATAAGCGCTG ACAATTCCAA AAACACAGCA TACCTGCAGA TGAACAGCCT GOCACOGRIGA TATTICGOGAC TOTTRAGGIT TITIGIGICOT AUGGACGICT ACTRIGICGGA > 3 니 띰 G r R A P м М M H W GICTICGITICC GITGIGCIAG ATACTIGGGCT TCAAGGICCT KEYY H Ē മ ß Ы

GACACTIGOGO ICTAITIAITIG IGCICGAGAC ACGGCCGCTT ACTITICACTA CIGGGGTICAA GGAACCCTIGG ICACCGTICIC CITCGGCCTICC CITCGGCCTICC AGTGGCAGAG GAGCCGGAGG CITCTGAGAGC AGTGGCAGAG GAGCCGGAGG ໝ N O I Ø × N T H S N G Z 3 SAD Α Ω н × TAA H R A А О A R D YDPK C K DTAV H GCGTGCTGAG A E 1901 110

æ

CCACGGACCA GITCCIGATG AAGGGGCTTG GCTGCCTGGT CAAGGACTAC TTCCCCGAAC TCTCGTGGAG ACCCCGTGT CGCCGGGACC COCTOCTICCA AGAGCACCTIC TGGGGGCACA GCGGCCCTGG GCCAGGAGGT S K ß Д CATCGGICTT CCCCCTGGCA GTAGCCAGAA GGGGGACCGT P L S < TGGTTCCCGG T K G P 2001 ACCAAGGCC 143

GAGTCCTGAG ATGAGGGAGT CGTCGCACCA TCAGGOGCC TGACCAGCGG CGTGCACACC TTCCCGGCTG TCCTACAGTC CTCAGGACTC TACTCCCTCA GCAGCGTGGT S < S Li × Ö ß GCACGTGTGG AAGGGCCGAC AGGATGTCAG വ O L F P A V V H T CAGCACCITIG AGTCCGCGGG ACTGGTCGCC Ö ß H SGAL GTCGTGGAAC N N 2101 CGGTGACGGT GCCACTGCCA V T V 177

TICCACCIGI ICITICAACI CGGGITTAGA TECAACETGA ATCACAAGCC CAGCAACACC AAGETGGACA AGAAAGTTGA GCCCAAATCT Q > CTGACACGGG AGATICGTCGA ACCCGTGGGT CTGGATGTAG ACGTTGCACT TAGTGTTCGG GTCGTTGTGG Z മ Ξ Z TCTAGCAGCT TGGGCACCCA GACCTACATC O E 2201 GACTGTGCCC ρ > 210

				17 /	21			
ACCCTCATGA TGGGAGTACT T L M I	AGGIGCATAA TCCACGIAIT V H N CAAGGAGIAC GITCCICAIG	ACAGGIGIAC ACCCIGCCCC TGICCACATG TGGGACGGGG Q V Y T L P P	GAGTGGGAGA GCAATGGGGA CTCACCCTCT CGTTACCCGT E W E S N G Q	ACAAGAGCAG GIGGCAGCAG IGITCICGIC CACCGICGIC D K S R W Q Q	TABATTAGCA TGCGACGGCC ATTTATTCGT ACGCTGCCGG L S P G K O	TTTATCACAG AAATAGIGIC	ATAGGCTTGG TATCCGAACC	TCATGCAATT ACTACGTTAA
ACCCAAGGAC TGGGTTCCTG P K D	GACGGCGTGG AGGTGCATAA CTGCCGCACC TCCACGTATT D G V E V H N GGCTGAATGG CAAGGAGTAC CCGACTTACC GTTCCTCATG	ACAGGIGIAC TGTCCACATG Q V Y	CAGTGGGAGA CTCACCCTCT E W E S			AATGCGGTAG TTACGCCATC	TGCTGTAGGC ACGACATCCG	CTATATGCGT GATATACGCA
	CIGGTACGIG GACCAIGCAC W Y V CACCAGGACT GIGGICCIGA H Q D	CCCGAGAACC GGGCICITGG R E P	CATCGCCGTG GTAGCGGCAC I A V	CTCACCGTGG GAGTGGCACC L T V	TGTCTCCGGG ACAGAGGCCC S L S	GATAAGCTTT CTATTCGAAA	TCACCCTGGA AGTGGGACCT	GCTGCTAGCG
GICTICCICT TCCCCCAAA CAGAAGGAGA AGGGGGGTTT V F L F P P K	TCAAGITCAA AGITCAAGIT K F N CACCGICCIG GIGGCAGGAC T V L	AAAGGGCAGC TTTCCCGTCG K G Q P	AAAGGCTTCT ATCCCAGCGA TTTCCCGAAGA TAGGGTCGCT K G F Y P S D	CTACAGCAAG GAIGICGITC YSK	AGCCTCTCCC TCGGAGAGGG	GCTTATCATC CGAATAGTAG	CATOGICATO CIOGGCACOS GIAGCAGIAG GAGOOGIGGO Coding Sequence	ACTATGGCGT TGATACCGCA
GGGACCGICA CCCIGGCAGI G P S	CICGGIGCTT CIGGGACICC AGTICAAGTIT S H E D P E V K F N TACCGIGIGG TCAGCGICCTG ATGGCACACC AGTICCAGGAC Y R V V S V L T V L	CTCCAAAGCC GAGGITTCGG S K A	AAAGGCTTCT TTTCCGAAGA K G F Y	AGGCTGCCGA GGAAGAAGGA GATGTCGTTC S D G S F F L Y S K	GGGAACGICT TCTCATGCTC CGTCATGCAT GAGGCTCTGC ACAACCACTA CACGCAGAAG CCCTTGCAGA AGAGTACGAG GCACTACGTA CTCCGAGACG TGTTGGTGAT GTGCGTCTTC G N V F S C S V M H E A L H N H Y	ATGITTGACA TACAAACTGT	ACAATGCGCT CATCGTCATC CTC TGTTACGCGA GTAGCAGTAG GAG Resistance Coding Sequence	ATCGCCAGTC TAGCGGTCAG
AACTCCTGGG TTGAGGACCC L L G	CICGGIGCIT C S H E 1 TACCGIGIGG T AIGGCACACC A	AGAAAACCAT TCITIIGGIA K T I	CTGCCTGGTC GACGGACCAG	TCCGACGGCT AGGCTGCCGA S D G	ACAACCACTA TGTTGGTGAT A L H	TTGTTAACTC AACAATTGAG	ACAATGCGCT TGTTACGCGA Resistance (TTCCGACAGC
CCAGCACCTG GGTCGTGGAC P A P E	ACCACCTGCA V D V CAACAGCAGG GITGTGGTGC N S T	GCCCCCATCG CGGGGGIAGC A P I E	TCAGCCTGAC AGTCGGACTG S L T	CGTGCTGGAC GCACGACCTG V L D	GAGGCTCTGC CTCCGAGACG H E A	GCGTTTTTTA CGCAAAAAAT	GAAATCTA CTTTAGAT SART TEL	ATAITCGICCA TAITAGCAGGI
CCCACCGTGC GGGTGGCACG P P C	GGGACTCCAG TGTACGCACC ACCACCTGCA PEVTCV VVDV AAGCCGCGG AGGAGCAGTA CAACAGCACG TTCGGCGCCC TCCTCGTCAT GTTGTCGTGC KPREEVV	AGCCCTCCCA TCGGGAGGGT A L P	AAGAACCAGG TTCTTGGTCC K N Q V	AACTACAAGA CCACGCCTCC CGTGCTGGACTG TTGATGTTCT GGTGCGGAGG GCACGACCTG N Y K T T P P V L D	CGTGATGCAT GCACTACGTA S V M	TAACGCTICGG TTGCCGCCGG GCGTTTTTTA ATTGCGAGCC AACGGCGGCC CGCAAAAAT	GGCACCGTGT CCGTGGCACA	CTCTTGCGGG
TGTGACAAAA CTCACACATG CCCACCGTGC CCAGCACCTG ACACTGTTTT GAGTGTGTAC GGGTGGCACG GGTCGTGGAC C D K T H T C P P C P A P E	GGGACTCCAG TGTACGCACC ACCACCTGCA P E V T C V V V D V AAGCCGCGG AGGAGCAGTA CAACAGCACG TTCGGCGCCC TCCTCGTCAT GTTGTCGTGC K P R E E Q Y N S T	AAGTGCAAGG TCTCCAACAA AGCCCTCCCA GCCCCCATCG TTCACGTTCC AGAGGTFGTT TCGGGAGGGT CGGGGGTAGC K C K V S N K A L P A P I E	AGAGATGACC AAGAACCAGG TCAGCCTGAC TCTCTACTGG TTCTTGGTCC AGTCGGACTG E M T K N Q V S L T	AACTACAAGA TTGATGITCT N Y K T	TCTCATGCTC AGAGTACGAG F S C	TAACGCTCGG	TTAAATTOCT AACGCAGTCA AATTTAACGA TTGCGTCAGT	ACTIGCCGGGC TGACGGCCCG
TGTGACAAAA CTCACACATG CCCACCGTGC CCAGCACCTG ACACTGTTTT GAGTGTGTAC GGGTGGCACG GGTCGTGGAC C D K T H T C P P C P A P E	ACCCAAGACA S R T TOCCAAGACA ACGCTTCTGT	AAGTGCAAGG TTCACGTTCC K C K V	2701 CATCCCGGGA AGAGATGACC AAGAACCAGG TCAGCCTGAC GTAGGGCCCT TCTCTACTGG TTCTTGGTCC AGTCGGACTG 377 S R E E M T K N Q V S L T	GCCGGAGAAC CGGCCTCTTG P E N	2901 GGGAACGICT TCTCATGCTC CGTCATGCAT GAGGCTCTGC ACAACCACTA CACGCAGAAG CCCTTGCAGA AGAGTAACGAG GCACTACGTA CTCCGAGACG TGFTGGTGAT GTGCGTCTTC 443 G N V F S C S V M H E A L H N H Y	3001 CIAGAGICCC TAACGCICGG TTGCCGCCGG GCGTTTTTA GAICTCAGGG ATTGCGAGCC AACGGCGGCC CGCAAAAAT	3101 TTAAATTGCT AACGCAGTCA GGCACCGTGT AN AATTTAACGA TTGCGTCAGT CCGTGGCACA TA ^St	3201 TTATIGOCGGT ACTIGOCGGC CTOTTIGOGGG ATATICGTOCA TTOCGACAGO ATOGOCAGTO ACTATIGGGGT GOTGOTAGOG CTATATIGOGT TGATIGOAATTA AATACGGOCA TGACGGCCA GACAAGGC TATATACGC TATAGCAGT AAGGOTGTOG TAGAGGTOGG TGATAACGCCA CGACGATOGC GATATAACGCA ACTAACGTTAA
2301	2401 277 2501 310		2701 377	2801	2901 (3001	3101	3201

FIG._21a

AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT CTCACAATTA ATTTAGGAGA TGCGGCCTGC GTAGCACCGC TCGAGCCATG GGCCCCTAGA TCCGGATTGC 1101 TCGCCCGTCA CAAAGAGCTT CAACAGGGGA GAGTGTTAAT TAAATCCTCT ACGCCGGACG CATCGTGGCG 226

21 18 / CGAGGCTTTC ATGACTAAAT GAAGTGGAGG AGAGAGGTGA GACCTCAGGG AAGAGCGAAG AGACCTAGGC CAAGACCCTG AGCTCGGTAC CCGGGGATCT AGGCCTAACG AGTGCATTTT TCCCATAGAT CTTAATACTT CTTCTTATAG CGTAAAGAAG AACGTAGATA CAAGCAAAAA AGATAACGAT GTTTGCGCAT GCGACTATAG 501 CAGTTGACCC AGTCCCCGAG CTCCCTGTCC GCCTCTGTGG GCGATAGGGT CACCATCACC TGCAGCGCAA GTCAGGATAT TAGCAACTAT TTAAACTGGT GTCAACTGGG TCAGGGGCTC GAGGGACAGG CGGAGACACC CGCTATCCCA GTGGTAGTGG ACGTCGCGTT CAGTCCTATA ATCGTTGATA AATTTGACCA 601 ATCAACAGAA ACCAGGAAAA GCTCCGAAAG TACTGATTTA CTTCACCTCC TCTCCACT CTGGAGTCCC TTCTCGCTTC TCTGGATCCG GTTCTGGGAC GGATTICACT CIGACCATCA GCAGICIGCA GCCAGAAGAC TICGCAACTI ATTACTGICA ACAGIATAGC ACCGIGCCGI GGACGITIGG ACAGGGIACC CCTAAAGTGA GACTGGTAGT CGTCAGACGT CGGTCTTCTG AAGCGTTGAA TAATGACAGT TGTCATATCG TGGCACGGCA CCTGCAAACC TGTCCCATGG TTCCACCTCT AGTTTGCTTG ACACCGACGT GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG ACGAAGACAA CACACGGACG GCCTGCGAAG TCACCCATCA GGGCCTGAGC CITAAGINGA AGAGGIANGA AACCIAINCC ITIANGICIG IACINITIAG AGIAACGACI CAACAAIAAA INCGAACGGG INTINCINCI ICICAGCINA GAACTGTGTG CGCAGGTAGA AGCTTTGGAG ATTATCGTCA CTGCAATGCT TCGCAATATG GCGCAAAATG ACCAACAGCG GTTGATTGAT CAGGTAGAGG GGGCTACGGT CGTAAGGACT GCTGCTATGC CTCGACGACG CGCTAATGCA TTTCTTCAAT AACTTCGTAG GAGCAGTCAT GTACGCAAGT TCACGTAAAA AGGGTATCTA GAATTATGAA GAAGAATATC GCATTTCTTC TTGCATCTAT GTTCGTTTTT TCTATTGCTA CAAACGCGTA CGCTGATATC GTGTGCCTGC CICCGGITIC AIGICACCII CCACCIAIIG CGGGAGGIIA GCCCAIIGAG GGICCICICA CAGIGICICG ICCIGICGII A D I Anti-VEGF Light chain^ CGGACGCTTC AGTGGGTAGT CAACTAACTA GGGCGCTGTA CGAGGTAAAG CCCGATGCCA GCATTCCTGA CGACGATACG GAGCTGCTGC GCGATTACGT AAAGAAGTTA TTGAAGCATC TTTTAATGTA TTTGTAACTA GAAAAGTIGI CGACAGIAIT ICAACAGIGC CGGCICIGAA IAICAGCGAA ACAAAAAIAA AAAAIIACAI AAACAIIGAI TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC GCCCTCCAAT CGGGTAACTC CCAGGAGAGT GTCACAGAGC 801 AAGGIGGAGA ICAAACGAAC IGIGGCIGCA CCAICIGICI ICAICITCCC GCCAICIGAI GAGCAGIIGA AAICIGGAAC IGCIICIGII SIATNAY S3 GACGITACGA AGCGITATAC CGCGITITIAC IGGITGICGC н О ន ភ ភ T V P E O L K CSAS TGTTTTTTT GGACAGCACC TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC CCTGTCGTGG ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG д V S A O K V Y 표 > SHIS GCTGTCATAA AGTTGTCACG GCCGAGACTT ATAGTCGCTT Y C S A S M T I ч ч ч т т у с F A T Y K A D Y A F L SLSASVGDRV N O N PGK APKV LIY FTS *STII Signal TIR ~1 CTTGACACAC GCGTCCATCT TCGAAACCTC TAATAGCAGT Q W W 면 더 K N H EAKV V A A S L S X TAGTIGICIT IGGICCITIT ACTTATTGAA GATAGGGTCT GCTCCALTIC AAAAGTTAAT CTTTTCAACA **X X** S P S LTI K V E I TTTCAATTA CCCGCGACAT Q Q 126 1001 901 301 401 101 201

1 GAATTCAACT TCTCCATACT TTGGATAAGG AAATACAGAC ATGAAAAATC TCATTGCTGA GTTGTTATTT AAGCTTGCCC AAAAAGAAGA AGAGTCGAAT

19/21 TGGATTAACA ACCTAATTGT TGAACAGCCT GCAACACCAA GGTGGACAAG GGGGTCAAGG AACCCTGGTC TTGGGACCAG TGCCTGGTCA CAGGACTCTA ACGGACCAGT TIGITCCTGTG CAGCITCTGG CTACGACITC ACGCACTACG GTATGAACTG GGTCCGTCAG GCCCCGGGTA AGGGCCTGGA ATGGGTTGGA CATACTTGAC CCAGGCAGTC CGGGGCCCAT TCCCGGACCT TACCCAACCT ATGGACGTCT GGGCCACAGC GGCCCTGGGC CCGGGACCCG CGTGGAACTC AGGCGCCCTG ACCAGCGGCG TGCACACCTT CCCGGCTGTC CTACAGTCCT GATGTCAGGA CGTTGTGGTT CCTATACCGG TGAACCGACC TATGCTGCGG ATTTCAAACG TCGTTTCACT TTTTCTTTAG ACACCTCCAA AAGCACAGCA TACCTGCAGA CCCCAGTTCC ტ ტ ტ ט > M Ö GACACTGCCG TCTATTACTG TGCAAAGTAC CCGTACTATT ACGGCACGAG CCACTGGTAT TTCGACGTCT CCCCGTGTCG TAAAGITIGC AGCAAAGIGA AAAAGAAAIC IGIGGAGGIT ITCGIGICGI CTGTGACGGC AGATAATGAC ACGTTTCATG GGCATGATAA TGCCGTGCTC GGTGACCATA AAGCTGCAGA TCCTGATGAA GGGGCTTGGC CACTGCCACA GCACCTTGAG TCCGCGGGAC TGGTCGCCGC ACGTGTGGAA GGGCCGACAG GTGTTCGGGT F D V W CTCCCTCAGC AGGGTGGTGA CTGTGCCCTC TAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT CACAAGCCCA T A р П STA P A V Ö A P G K Ö CCCTGGCACC CTCCTCCAAG AGCACCTCTG TCGTGGAGAC SAGGGAGTCG TCGCACCACT GACACGGGAG ATCGTCGAAC CCGTGGGTCT GGATGTAGAC GTTGCACTTA S N H W Y H T H ^Anti-VEGF Heavy Chain F S L D AGCCAGAAGG GGGACCGTGG GAGGAGGTTC ۷ ۲۵ ۲۵ G T S S S R н PYYY MNM R F L A P G A I Ö SVFP TGCGTGATGC TCGGTCTTCC F K R A K Y T H Y VTVS YAAD GTCGAAGACC GATGCTGAAG CGGCCTCCAC CAAGGGCCCA GGATATGGCC ACTTGGCTGG ATACGACGCC GCCGGAGGTG GTTCCCGGGT AGGACTACTT CCCCGAACCG GTGACGGTGT YY പ Y D F д ĸ DTAV **დ** S д Æ æ GCGCGCTGAG TGGCAGAGGA AACAGGACAC CGCGCGACTC ACCGTCTCCT 臼 1701 1801 1901 110 2001 143 2101 210 177

ACGTAGATAC AAGCAAAAA GATAACGATG TTTGCGCATG CGACTCCAAG TCGACCACCT CAGACCGCCA CCGGACCACG TCGGTCCCCC GAGTGAGGCA 1601 TGCATCTATG TTCGTTTTTT CTATTGCTAC AAACGCGTAC GCTGAGGTTC AGCTGGTGGA GTCTGGCGGT GGCCTGGTGC AGCCAGGGGG CTCACTCCGT 'STII Signal TIR-1 G ^ T G G G ಭ L V E œ A E V ď Z ď н >

K N I A

CTGCTATGCC CCGAGACTTA ATCAGCGAAA CAAAAATAAA AAATTACATA AACATYGATC ATGCGTYCAA GTGCATYTYT CCCATAGATC TYAATACTYC TYCTTATAGC GTAAAGAAGA GCCGGGCGTT TITIATIGIT GCCGACGCGC ATCTCGAATG AACTGTGCC GCAGGTAGAA GCTTTGGAGA TTATCGTCAC TGCAATGCTT CGGCCCGCAA AAAATAACAA CGGCTGCGCG TAGAGCTTAC TTGACACACG CGTCCATCTT CGAAACCTCT AATAGCAGTG ACGTTACGAA GACGATACGG CACGTAAAAA GGGTATCTAG AATTATGAAG AAGAATATCG CATTTCTTCT CTGTCATAAA GTTGTCACGG GGCTACGGTC GTAAGGACTG GACAGTATTT CAACAGTGCC CCGATGCCAG CATTCCTGAC CGATTACGTA AAGAAGTTAT TGAAGCATCC TCGTCAGTAA AAAGTTAATC TTTTCAACAG CTCCATTTCG GCTAATGCAT TICTICAATA ACTICGTAGG AGCAGICATT TITCAATTAG AAAAGTIGIC GAGGTAAAGC CCGCGACATG GGCGCTGTAC TTGATTGATC AGGTAGAGGG TCCATCTCCC TITAATGTAT ITGTAACTAG TACGCAAGIT AACTAACTAG CCAACAGCGG CGCAAAATGA GCGTTTTACT GTTTTTTTT CTCGGTTGCC GAGCCAACGG CGCAATATGG AGCTGCTGCG SCGTTATACC TCGACGACGC TAGTCGCTTT 1401 1501 1301

20 / 21 CGAGAACCAC REPO TCGCCGTGGA GGTCGCTGT AGCGGCACCT ACAGCAAGCT CACCGTGGAC TGCGGAGGGC ACGACCTGAG GCTGCCGAGG AAGAAGGAGA TGTCGTTCGA GTGGCACCTG CGGTGCTTCT GGGACTCCAG TTCAAGTTGA CCATGCACCT CCGTCCTGCA CCAGGACTGG GGTCCTGACC GCTCTTGGTG TCTCCGGGTA GCGTCTTCTC GCAGAGGGAC AGAGGCCCAT TTAITICGTAC GCTGCCGGGA TCTCAGGGAT TGCGAGCCAA CGGCGGCCCG CAAAAATAA CAATTGAGTA CAAACTGTCG AATAGTAGCT ATTCGAAAIT TGCGGTAGTT TATCACAGTT AAATTGCTAA CGCAGTCAGG CACCGTGTAT GAAATCTAAC AATGCGCTCA TCGTCATCCT CGGCACCGTC ACCCTGGATG T V D A V K F N W GGCAGGACGT CCAAAGCCAA AGGGCAGCCC TITITGGIAGA GGITITCGGIT ICCCGICGGG CCCAGCGACA TCATGCTCCG TGATGCATGA GGCTCTGCAC AACCACTACA CGCAGAAGAG CCTCTCCCTG SDI CGACGGCCCT AGAGTCCCTA ACGCTCGGTT GCCGCCGGGC GTTTTTATT GTTAACTCAT GTTTGACAGC TTATCATCGA S K L V L H д О FFLY CCAAGACAAA GCCGCGGGAG GAGCAGTACA ACAGCACGTA CCGTGTGGTC AGCGTCCTCA GGCACACCAG TCGCAGGAGT SVLT GCCTGGTCAA AGGCTTCTAT CGGACCAGTT TCCGAAGATA CGGAGAACAA CTACAAGACC ACGCCTCCCG TGCTGGACTC CGACGGCTCC TTCTTCCTCT M S K A K P E V G Fi KTIS TTGGTGATGT NHYT CTGAATGGCA AGGAGTACAA GTGCAAGGTC TCCAACAAAG CCCTCCCAGC CCCCATCGAG AAAACCATCT HED L V K R V V О С С SLTC VOVS TGTCGTGCAT CCTGCCCCCA TCCCGGGAAG AGATGACCAA GAACCAGGTC AGCCTGACCT TCGGACTGGA CCGTCGTCCC CTTGCAGAAG AGTACGAGGC ACTACGTACT CCGAGACGTG GGGAGGGTCG GGGGTAGCTC Y T L D H H A L H മ ТРРV CTCGTCATGT EQYN TCTACTGGTT CTTGGTCCAG Ы М C < > O N ы × SNKA CGGCGCCCTC AGGTTGTTTC GATGTTCTGG T X 四 マ 다 도 된 Y K T × SRTP GGTTCTGTTT CACGTTCCAG AGGCCCTTC GCCTCTTGTT GGCAGCAGGG GAACGTCTTC N C K < S R E × TCCTCATGTT GTGCATAATG CACGTATTAC GGACGGGGGT **AATGGGCAGC** TTACCCGTCG K K I W 闰 2701 AGGTGTACAC 3001 AATAAGCATG CGGCGTGGAG TCCACATGTG GTGGGAGAGC TTCTCGTCCA GACTTACCGT GCCGCACCTC CACCCTCTCG 2901 AAGAGCAGGT 2501 343 310 2601 2801 3101 277 377 410 443 477

FIG._21c

GACATCCGTA TCCGAACCAA TACGGCCATG ACGGCCCGGA GAACGCCCTA TAGCAGGTAA GGCTGTCGTA GCGGTCAGTG ATACCGCACG ACGATCGCGA

3301

3201 CTGTAGGCAT AGGCTTGGTT ATGCCGGTAC TGCCGGGCCT CTTGCGGGAT ATCGTCCATT CCGACAGCAT CGCCAGTCAC TATGGCGTGC TGCTAGCGCT

ACGCCATCAA ATAGTGTCAA TTTAACGATT GCGTCAGTCC GTGGCACATA CTTTAGATTG TTACGCGAGT AGCAGTAGGA GCCGTGGCAG TGGGACCTAC

AStart Tet Resistance Coding Sequence

2301 AAAGTTGAGC CCAAATCTTG TGACAAAACT CACACATGCC CACCGTGCCC AGCACCTGAA CTCCTGGGGG GACCGTCAGT CTTCCTCTTC CCCCAAAAC

TITCAACICG GGITIAGAAC ACIGITITIGA GIGIGIACGG GIGGCACGGG ICGIGGACIT GAGGACCCCC CIGGCAGICA

2401 CCAAGGACAC CCTCATGATC TCCCGGACCC CTGAGGTCAC ATGCGTGGTG GTGGACGTGA

D R

243

GGAGTACTAG AGGGCCTGGG GACTCCAGTG TACGCACCAC

GGTTCCTGTG

GGTACGTGGA

GCCACGAAGA CCCTGAGGTC AAGTTCAACT

CACCTGCACT

ນ ຂ

L G

A P E

ص ص

Д

GAAGGAGAAG



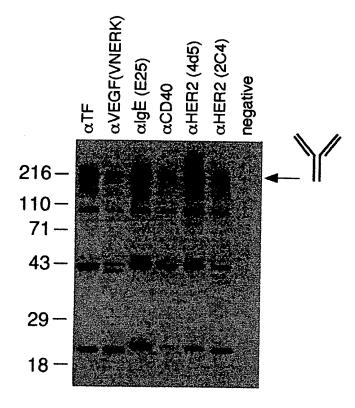


FIG._22A

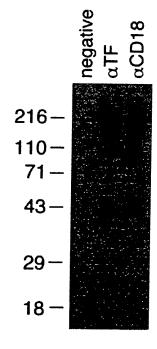


FIG._22B